

Reproductive hormonal treatments for mood disorders in women

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There has been a century-long view in medicine that reproductive function in both men and women is intimately involved with mood regulation. The 19th century witnessed a proliferation of medical reports documenting beneficial effects on mood and behavior after medical or surgical manipulations of women's reproductive function. More recently, the results of several studies suggest that gonadal steroids do regulate mood in some women. Thus, there is considerable interest in the potential role of reproductive therapies in the management of depressive illness, including both classical and reproductive endocrine-related mood disorders. Future studies need to determine the predictors of response to hormonal therapies compared with traditional antidepressant agents, and to characterize the long-term safety and benefits of these therapies.

Dialogues Clin Neurosci. 2002;4:211-223.

Keywords: *women; depression; estrogen; progesterone; DHEA; antidepressants*

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Over a century ago, numerous case reports described the onset of mood and behavioral disorders in temporal association with altered reproductive function, as well as the dramatic remission of mood and behavioral symptoms following the resumption of normal menstruation. Indeed, treatment strategies frequently included efforts to either normalize menstruation or remove the reproductive organs of women with mental illness. Although interest in reproductive endocrine therapies for mood disorders has persisted throughout the past century, the specific role, if any, that reproductive endocrine interventions should play in the treatment of mood disorders is still unclear.

In this article, we will describe the recent history of reproductive endocrine therapies for mood disorders, review the biology of gonadal steroids that may be relevant to mood regulation, discuss the current role for reproductive endocrine therapies in both reproductive endocrine-related mood disorders and classical mood disorders, and review theories about the mechanisms of action of gonadal steroids in the treatment of these conditions. Finally, we will discuss the potential future role of these and related compounds in the treatment of mood disorders.

Background

The 19th century medical literature contained several presumptions about the pathophysiology of mood disorders in women largely based on anecdotal observations of reproductive endocrine dysfunction (eg, amenorrhea) in psychiatrically ill women.¹⁻⁵ These inferences, in turn, were translated into therapeutics. Thus, numerous reports also documented the beneficial effects on mood and behavior associated with medical or surgical manipulations of a woman's reproductive function.⁶⁻⁹ In addition to their interest in the role of reproductive function in psychiatry, medical researchers in the late 19th

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Selected abbreviations and acronyms

BDNF	<i>brain-derived neurotrophic factor</i>
CREB	<i>cyclic adenosine monophosphate response element-binding (protein)</i>
DHEA	<i>dehydroepiandrosterone</i>
ECT	<i>electroconvulsive therapy</i>
ERT	<i>estrogen replacement therapy</i>
FSH	<i>follicle-stimulating hormone</i>
GnRH	<i>gonadotropin-releasing hormone</i>
5-HT	<i>serotonin (5-hydroxytryptamine)</i>
OC	<i>oral contraceptive</i>
PMS	<i>premenstrual syndrome</i>
PPD	<i>postpartum depression</i>
SSRI	<i>selective serotonin reuptake inhibitor</i>

century also developed an interest in glandular secretions and factors that potentially modify physiology.¹⁰ Early experiments in humans with preparations derived from animal glands including thyroid, adrenal, ovary, testes, and spleen provided the directions for the developing fields of endocrinology and immunology. In his seminal lecture in 1889, Brown-Séquard¹¹ not only originated the formal study of endocrinology, but he reported the potential psychotropic effects of gonadal secretions. His description of the invigorating effects of testicular extracts resulted in a brief but widespread use of these compounds (as well as other interventions intended to increase the body's testicular or seminal fluid levels) in a variety of therapeutic settings.¹²⁻¹⁴ In addition to extracts of both testes and ovaries, investigators experimented with extracts of the thyroid and adrenal glands in psychiatric patients.¹⁰ This interest in thyroid and adrenal extracts enjoyed more enduring success with the recognition of their beneficial effects in the treatment of myxedema and Addison's disease, respectively.¹⁵ However, the widespread use of gonadal extracts ultimately met with criticism due to some disappointing results and the realization that these extracts were not the "fountain of youth." Their subsequent clinical use was largely restricted to the treatment of menopause-related hot flashes (ovarian extracts).¹⁶ Nonetheless, the observation that ovarian extracts inhibited ovulation in rabbits was sufficient to maintain medical interest in the potential role of gonadal extracts for the control of human fertility.¹⁷

Efforts to improve techniques of extraction and purification of biologically active substances from the gonads

were fueled by the hope that factors regulating reproductive function would be identified. By the late 1920s and early 1930s through the efforts of Allen and Doisy,¹⁸ Corner and Allen,¹⁹ as well as others, many gonadal steroids were isolated and characterized including estrone, estradiol, progesterone, and several androgens. Moreover, during the next 10 years, chemists identified modifications of the steroids that could alter their absorption (eg, acetylation) and potency (eg, addition of ethinyl group or removal of C-19 methyl group). These findings initiated a resurgence in the medical use of gonadal steroids.²⁰⁻²³ Estrogen replacement therapy (ERT) was used to treat menopausal symptoms in the 1930s, and oral contraceptives (OCs) were developed and first approved (ie, Enovid[®]) by the Food and Drug Administration (FDA) in 1960. The use of exogenous gonadal steroids in women was once again widespread, and several papers were published reporting the therapeutic benefits of these compounds in involuntarily melancholia,^{24,25} premenstrual syndrome (PMS),^{26,27} and postpartum depression (PPD).²⁸⁻³⁰ However, their widespread usage was restricted after reports in the 1970s of increased rates of endometrial cancer secondary to unopposed ERT and increased rates of thrombosis and pulmonary emboli in women taking OCs.^{23,31} More recently, gonadal steroid therapy has gained popularity due in part to the reports of the enhanced safety of both ERT and OCs and the reported beneficial/disease protective effects of gonadal steroids on multiple organ systems including the musculoskeletal, cardiovascular, and central nervous systems.³²⁻³⁶ The discovery of several other factors involved in the control of reproduction also led to new drug development. The decapeptide gonadotropin-releasing hormone (GnRH) was isolated and sequenced in the 1970s, and the observation that continuous GnRH infusion resulted in the downregulation of pituitary GnRH receptors led to the development of several GnRH agonists.^{37,38} These agonists were used to suppress reproductive endocrine function in a variety of medical conditions including hormone-dependent cancers and endometriosis.^{39,40} In combination with gonadal steroids, preparations of GnRH agonists provided physicians with a strategy to control reproductive function and regulate the exposure to specific gonadal steroids without resorting to surgery. Thus physicians could selectively eliminate and/or replace reproductive factors considered to be the potential source of a medical or psychiatric problem.

Could gonadal steroids be involved in mood regulation?

Results from animal studies demonstrate that gonadal steroids influence several of the neuroregulatory systems thought to be involved in both the pathophysiology of affective disorders and the efficacy of antidepressant therapies.⁴¹⁻⁴⁵ In some, but not all,⁴⁶ experimental paradigms, estradiol has been observed to inhibit serotonin reuptake transporter (SERT) mRNA⁴⁷ and decrease activity at serotonin (5-hydroxytryptamine) 5-HT_{1A} receptors,^{48,49} consistent with some reported actions of antidepressants on serotonergic system function. Moreover, in one study estradiol and testosterone facilitated imipramine-induced downregulation of 5-HT₂ receptors in the rat frontal cortex.⁵⁰ In addition to classic neurotransmitter systems, several candidate neural signaling systems have been identified as potential mediators of the therapeutic actions of antidepressants and electroconvulsive therapy (ECT) (eg, cyclic adenosine monophosphate [cAMP] response element-binding [CREB] protein and brain-derived neurotrophic factor [BDNF])⁵¹⁻⁵⁴ based on observations that these systems are modulated by a range of therapies effective in depression (eg, serotonergic and noradrenergic agents and ECT) and exhibit a pattern of change consistent with the latency to therapeutic efficacy for most antidepressants.⁵⁵ For example, antidepressants increase the expression and activity of CREB in certain brain regions (eg, hippocampus)⁵⁶ and regulate (in a brain region-specific manner) activity of genes with a cAMP response element.⁵⁵ Genes for BDNF and its receptor trkB have been proposed as potential targets for antidepressant-related changes in CREB activity.^{55,57} Similarly, estradiol has been reported to influence many of these same neuroregulatory processes. Specifically, ovariectomy has been reported to decrease, and estradiol increase, BDNF levels in the forebrain and hippocampus.^{58,59} Estrogen also increases CREB activity^{60,61} and trkA⁶² in the rat brain. In contrast, an estradiol-induced decrease in BDNF has been reported to mediate estradiol's regulation of dendritic spine formation in hippocampal neurons.⁶³ Thus, the therapeutic potential of gonadal steroids in depression is not only suggested by their widespread actions on neurotransmitter systems, but also by certain neuroregulatory actions shared by both estrogen and traditional therapies for depression (ie, antidepressants, ECT).

Gonadal steroids in the treatment of mood disorders

Reproductive endocrine-related mood disorders

Reproductive endocrine-related mood disorders refer to depressive-like disorders in which the appearance of mood disturbances occurs in temporal association with a change in reproductive function, and includes mood disorders occurring in association with the luteal phase of the menstrual cycle, the postpartum, and the perimenopause. Given the apparent association between the onset of mood disturbance and the change in reproductive function, these conditions have been suggested to develop secondary to some abnormality in ovarian hormone secretion, and reproductive therapies have been used in an attempt to correct the presumed endocrine anomaly.⁶⁴

Premenstrual syndrome

PMS is a condition characterized by cyclic changes in symptoms (including irritability, sadness, and anxiety) that interfere with daily function and are confined to the luteal phase of the menstrual cycle, with symptom remission occurring within a few days of the onset of menses.⁶⁵ No diagnosis-related differences in reproductive hormones have been consistently observed during the luteal phase that would distinguish a woman with PMS from a woman without PMS.⁶⁶ Despite the lack of evidence of ovarian dysfunction in women with PMS, the association of PMS symptoms with the luteal phase of the menstrual cycle perpetuated clinicians' views that an abnormality of corpus luteum function caused PMS. Thus, multiple trials were conducted involving the administration of progesterone or progestin in women with PMS.⁶⁷ However, the widespread use of progesterone in women with PMS was considerably diminished by the results of several recent studies: first, two large double-blind, placebo-controlled trials of natural progesterone (both suppository and oral forms) definitively demonstrated the lack of efficacy of progesterone compared with placebo in PMS.^{68,69} Second, a study employing a progesterone receptor antagonist, RU-486, with or without human chorionic gonadotropin, demonstrated that the normal symptoms of PMS could occur independently of the luteal phase of the menstrual cycle⁷⁰ and, therefore, a luteal phase abnormality as a cause of PMS was no longer tenable.

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The belief that PMS reflected a disturbance in ovarian function led to several trials of OCs to suppress or regulate ovarian function in this condition. Earlier cross-sectional studies suggested that women using OCs experienced fewer PMS symptoms than nonusers.⁷¹⁻⁷³ However, studies also reported the opposite,⁷⁴ and most results demonstrated that women on OCs reported fewer physical symptoms (ie, breast pain, bloating), but did not report fewer or less severe mood symptoms than nonusers.⁷⁵⁻⁷⁷ In fact, similar prevalence rates of cyclic mood symptoms regardless of OC use were prospectively documented by Sveindottir et al,⁷⁸ with 2% to 6% of women meeting criteria for severe PMS in both OC users and nonusers. Moreover, observations suggest that the severity of mood symptoms do not vary with different preparations of OCs (eg, monophasic versus triphasic)^{79,80}; however, one study did observe that the progestin desogestrel (reported to have less androgenic activity) was associated with fewer mood symptoms than levonorgestrel.⁸¹ Despite similar prevalence rates of negative mood symptoms in OC users and nonusers, some clinic-based studies suggested that a subgroup of women with PMS reported an improvement in mood symptoms while on OCs.⁸²⁻⁸⁷ None of the recent controlled trials of OCs in PMS have observed significant improvement (or worsening) in mood symptoms relative to placebo.⁸⁸⁻⁹⁰ However, these trials did observe significant reductions in symptom severity on OCs compared with placebo for some physical and behavioral symptoms, including loss of libido,⁸⁹ breast pain, and bloating,⁸⁸ and increased appetite and food cravings.⁹⁰ Thus, neither cross-sectional studies nor controlled trials support a role for any formulation of OCs (tested to date) in the treatment of PMS.

Investigators have also examined the efficacy in PMS of estradiol (without the progestin contained in OCs) or testosterone. Trials of supraphysiologic doses of estradiol with or without testosterone have documented beneficial effects compared with placebo in women with PMS.⁹¹⁻⁹³ Preliminary reports suggest that lower (more physiologic) doses of testosterone alone may also be effective in the treatment of PMS.⁹⁴⁻⁹⁶ Lower doses of estrogen, however, are no more effective than placebo⁹⁷ and, therefore, it is possible that the therapeutic benefits of the higher dose estrogens are secondary to the suppression of ovulation.⁹³ Nevertheless, one cannot infer the efficacy of these compounds to be secondary to ovarian suppression alone, given the lack of efficacy of

OCs, which also inhibit ovulation, and the reported efficacy of compounds such as danazol⁹⁸ when administered after ovulation in at least one study.⁹⁹

Several open trials of ovarian suppression, induced surgically or medically, have reported the beneficial effects of this strategy in the treatment of PMS.¹⁰⁰⁻¹⁰⁷ Most,¹⁰⁸⁻¹¹¹ but not all,^{112,113} placebo-controlled trials of GnRH agonists (eg, leuprolide acetate) in PMS have reported the therapeutic efficacy of GnRH agonist-induced ovarian suppression compared with placebo. We observed significant reductions in PMS symptom severity during leuprolide treatment for all symptoms measured.¹¹⁴ In many of the trials, the degree of individual response to GnRH agonist varied considerably, despite evidence of a beneficial response to ovarian suppression on a group basis. We observed a response rate of approximately 60% employing relatively conservative criteria (ie, the absence within a 2-month time period of 2-weekly mean scores on anxiety, depression, or irritability greater than 2.5 on a 6-point scale).¹¹⁴ Similarly, Freeman et al reported that 67% of women with PMS responded to GnRH agonist-induced ovarian suppression.¹⁰⁹ Response rates did not differ depending on the presence or absence of a past history of affective disorder in our sample of women with PMS. However, Freeman et al observed that the presence of persistent depressive symptoms throughout the menstrual cycle was associated with non-response to GnRH agonists.¹⁰⁹ The reported response rates to selective serotonin reuptake inhibitors (SSRIs) in women with PMS (40%–60%)¹¹⁵⁻¹²² appear similar to the rates observed in trials of GnRH agonists. Thus, although the majority of studies would support the short-term use of GnRH agonists or SSRIs in this condition, symptomatic response is not uniform even to complete ovarian suppression. Moreover, it has not been determined whether the group of women with PMS who are responsive to SSRIs differs from those responsive to hormonal therapies. The factors that predict response to both therapies need to be identified, and these data may reveal further information about the pathophysiology of PMS.

The possibility that PMS reflects an abnormal mood and behavioral response to normal changes in ovarian steroid secretion has been suggested by several studies.^{102,114,123-126}

We observed the precipitation of typical PMS symptoms after the administration of physiologic doses of either estradiol or progesterone in a group of women whose PMS symptoms were otherwise eliminated by ovarian

suppression with a GnRH agonist.¹¹⁴ Asymptomatic women who had no history of PMS undergoing the same hormonal manipulations showed no disturbance of mood during either hypogonadal conditions or hormonal addback. It would appear, therefore, that women with PMS are differentially sensitive to the mood-perturbing effects of gonadal steroids, as similar steroid manipulations in women without a history of PMS were without effect on mood.

The efficacies of both GnRH agonists and high-dose estrogen therapy in the treatment of PMS and the lack of efficacy of most OCs suggest that continuous steady-state levels of gonadal steroids may prevent the cyclic symptoms of PMS. Thus, the prolonged use of active OCs continuously may provide an additional treatment for some women with PMS. Nevertheless, typical PMS symptoms would be predicted to emerge if hormones are withdrawn and then readministered. Trials of steady-state hormonal therapy are underway and may lead to an effective treatment for PMS as an alternative to traditional SSRIs.

Perimenopausal depression

Perimenopausal depression is a condition defined by the onset of depression at middle age in association with the onset of menstrual cycle irregularity or amenorrhea. Perimenopausal reproductive status is confirmed by the presence of menstrual cycle irregularity (or amenorrhea of less than 1 year's duration) and hormonal evidence of ovarian dysfunction. This latter criterion has been operationalized to include either a single elevated plasma follicle-stimulating hormone (FSH) level or more persistent elevations of plasma FSH levels (eg, three out of four ≥ 14 IU/L).¹²⁷ *The Diagnostic and Statistical Manual of Mental Disorders* 4th edition (*DSM-IV*)¹²⁸ includes neither perimenopausal depression as a distinct mood disorder nor the perimenopause as a course specifier (as it does the postpartum period). Perimenopausal depressions may not be distinguished from major depressive disorder on the basis of phenomenology, course, family, or personal history of mood disorder, but they do appear to be distinct in their treatment response characteristics; specifically, they are responsive to ERT in contrast to depressions either before or after the perimenopausal phase.^{129,130}

Despite the coincident timing of the onset of depression and the perimenopause, there has been no consistent

evidence suggesting that perimenopausal depressed women can be distinguished from asymptomatic perimenopausal women on the basis of abnormalities of ovarian estrogens or androgens.¹³¹ Nonetheless, there have been several therapeutic trials of ERT in perimenopausal and postmenopausal women with depression.

Controlled studies employing synthetic forms of estrogen in the treatment of depression have yielded mixed results. Estrogen has been reported to improve mood (albeit inconsistently)¹³²⁻¹³⁴ in the following samples: (i) perimenopausal and postmenopausal women reporting depressive symptoms¹³⁵⁻¹³⁷; (ii) postmenopausal women with depression unresponsive to traditional antidepressant therapy¹³⁸; and (iii) nondepressed menopausal women not experiencing hot flashes.¹³⁹

We examined the therapeutic efficacy of estradiol replacement in 34 women (approximately half of whom had no prior history of depression) with perimenopausal depression under double-blind, placebo-controlled conditions.¹²⁹ After 3 weeks of estradiol, depression rating scale scores were significantly decreased compared with baseline scores and significantly lower than scores in the women receiving placebo. A full or partial therapeutic response was seen in 80% of subjects on estradiol and in 22% of those on placebo, consistent with the observed effect size in a recent meta-analysis of studies examining estrogen's effects on mood.¹⁴⁰ The therapeutic response to estrogen was observed in both major and minor depression as well as in women with and without hot flashes. Finally, neither baseline nor posttreatment estradiol levels predicted therapeutic response. These data suggest that estrogen's effect on depression is not solely a product of its ability to reduce the distress of hot flashes.

Our findings are consistent with data from Montgomery et al¹³⁵ and Saletu et al¹³⁶ suggesting the beneficial effects of estrogen on mood in perimenopausal women reporting depressive symptoms. Two recent studies, by Soares et al¹³⁰ and Morrison et al (personal communication) have extended these observations. First, Soares et al reported a significant and beneficial effect of ERT compared with placebo in women with perimenopause-related major depression (as defined by the Primary Care Evaluation of Mental Disorders [PRIME-MD])¹⁴¹ and, additionally, reported that baseline plasma estradiol levels did not predict response to estrogen treatment.¹³⁰ Second, Morrison et al observed that estrogen was no more effective than placebo in postmenopausal

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depressed women in contrast to previous results in perimenopausal women. These data emphasize that the stage of reproductive senescence may predict response to estrogen, as originally reported by Appleby et al.¹⁴² Thus, perimenopausal women who are undergoing changes in reproductive function may be more responsive to estrogen than postmenopausal women whose hormonal changes have long since stabilized.

Postpartum depression

PPD is defined in the *DSM-IV*¹²⁸ as the onset of a depressive disorder within 4 weeks after delivery. The symptoms of depression during the postpartum are not distinct from depressions occurring at other periods of life, and the temporal association of symptoms with the postpartum period is the critical diagnostic feature, similar to perimenopausal depression. PPDs are not associated with an abnormality of reproductive function¹⁴³; nonetheless, women with a history of PPD display an abnormal mood response to changes in reproductive hormones simulating endocrine events occurring at delivery.¹⁴⁴ Despite the absence of endocrine abnormalities in this condition, there has been interest in whether supplementing reproductive endocrine function during the immediate postpartum could prevent or diminish depression.

Open studies of progesterone for the treatment of PPD were conducted by Dalton,¹⁴⁵ who reported a reduced recurrence rate of postnatal depression in women using prophylactic progesterone compared with untreated women.¹⁴⁶ Nonetheless, as with studies of progesterone in PMS, the absence of controlled trials examining the efficacy of progesterone in PPD limited the utility of Dalton's observations. In fact, one double-blind, placebo-controlled study of 180 postpartum women, treated with either norethisterone enanthate or placebo, showed an increased risk of developing depressive symptoms following treatment with norethisterone.¹⁴⁷ Thus, as with PMS, current evidence does not support a role for progesterone in the treatment of PPD.

Similar to earlier reports of progesterone's efficacy, an open trial in women at risk for puerperal psychosis demonstrated that high-dose estrogen treatment resulted in a lower than expected 1-year relapse rate (9% compared with an expected 35%–60% without prophylaxis).¹⁴⁸ Varying doses of estrogen (Premarin® ranging in dose from 0.625 to 10 mg per day or IV estradiol 25 mg

every 8 hours) were administered immediately postpartum and then tapered over 4 weeks. It was suggested that estrogen administration could attenuate the rapid puerperal drop in estradiol levels, thereby reducing the negative impact of the postpartum “estrogen withdrawal state” on mood. In a follow-up study, Gregoire et al¹⁴⁹ tested the suggestion that estradiol withdrawal caused PPD in a double-blind, placebo-controlled study of estradiol in 61 women who developed major depression within 3 months of delivery. Eighty percent of the patients receiving estrogen patch experienced a significant reduction in depression severity after 3 months of treatment, compared with 31% of the placebo-treated group. Reductions in mood symptoms on estrogen therapy were observed in women regardless of concurrent antidepressant use, and estrogen's antidepressant effects were rapid and observed after 2 to 3 weeks of treatment. A similar rapid response to estradiol was also recently reported in an open-label trial of sublingual estradiol,¹⁵⁰ similar to the timing of the response to estradiol in perimenopausal depression.

Classical mood disorders

In contrast to reproductive endocrine-related mood disorders, classical mood disorders, with few exceptions, have a more tenuous relationship with reproductive endocrine change. Several relationships have been proposed to explain reported observations. First, alterations in reproductive function may modulate the course or appearance of mood disorders. For example, investigators have described the menstrual cycle-related exacerbation or modulation of the symptoms of depressive and anxiety disorders, as well as bipolar illness.¹⁵¹ It is possible, therefore, that reproductive therapies would influence the course of these conditions.¹⁵² Indeed, clinical anecdotes describe the therapeutic benefits of ovarian suppression with GnRH agonists in women with menstrual cycle-entrained rapid cycling bipolar illness. Second, the hormonal accompaniments of aging, some of which involve reproductive hormones, may influence the onset of depression. Late- and midlife-onset depressions occur in the context of declining adrenal androgen secretion and reproductive senescence, and, therefore, the replacement of these reproductive hormones in late- and midlife-onset depressions may have a role in their treatment.¹⁵³⁻¹⁵⁵ Finally, gonadal steroids may modify the treatment response characteristics of subjects treated with conventional antidepressants. Some^{156,157} but not all¹⁵⁸

studies have reported that the administration of estrogen enhances the therapeutic response to certain psychotropic agents including SSRIs. Additionally, altered reproductive endocrine function may result in disturbances in certain target symptoms, such as loss of libido,¹⁵⁹ that occur in association with depression, but are not part of its presentation. Such symptoms, for example, may be responsive to androgen replacement but not antidepressant therapy. Similarly, androgen therapy may be effective in treating loss of libido occurring as a side effect of antidepressants.¹⁶⁰

Midlife depression

Midlife in both men and women is characterized by a steady decline in the production of androgens such as dehydroepiandrosterone (DHEA) and androstenedione, which are mostly of adrenal origin yet contribute up to 50% to circulating androgen levels (testosterone, dihydrotestosterone) in women.^{155,161,162} Declining plasma levels of testosterone in aging women may be less dramatic due to continued secretion of testosterone by the postmenopausal ovary.¹⁶³ We examined the effects of the adrenal androgen DHEA on mood in women with midlife-onset depression in a double-blind, placebo-controlled, crossover design study. Preliminary results are consistent with previous studies by Wolkowitz et al¹⁶⁴ and suggest the antidepressant efficacy of DHEA: DHEA, but not placebo, significantly improved depression ratings after 6 weeks of treatment¹⁶⁵ (Daly et al, unpublished data). Plasma testosterone levels increased by approximately 30% after DHEA treatment (Smith et al, unpublished data). However, baseline plasma levels of DHEA or metabolites of DHEA (estradiol and testosterone) and mood were not correlated, and the lack of correlations between therapeutic response and baseline DHEA levels emphasizes our inability to infer that midlife depression in any way reflects a deficiency of reproductive hormones (Daly et al, personal communication).

Mood disorders in the context of medical illness

Several studies have suggested a potential role of hypogonadism in the mood symptoms and low energy present in some women with human immunodeficiency virus (HIV) infection.¹⁶⁶⁻¹⁶⁸ Trials of DHEA in women and other androgens such as testosterone in men with HIV have reported mood improvements.^{166,169,170} Although these

reports may suggest a psychotropic effect of gonadal steroids in these subjects, the improved mood may also reflect the anabolic effects of these steroids. Improved muscle strength and weight changes in these subjects may improve energy level and, therefore, indirectly improve mood.^{170,171}

Potential mechanisms of antidepressant action of gonadal steroids

Several mechanisms may underlie the antidepressant effects of reproductive therapies in women. First, gonadal steroid supplements may correct a pathological deficiency of a particular gonadal steroid. However, in the majority of studies where gonadal steroids have been reported to be effective, the condition is neither associated with a particular abnormality of reproductive hormones nor are levels of reproductive hormones predictive of subsequent response to the therapeutic intervention. Nonetheless, local tissue metabolism of gonadal steroids (eg, aromatization of androgens) may produce a wide range of gonadal steroid levels within specific tissues. Thus, local and tissue-specific “relative” deficiencies of reproductive hormones could exist and cause symptoms, but not be identified by simply measuring plasma hormone levels. Second, studies of the effects of ERT in osteoporosis¹⁷² suggest the presence of a threshold of circulating estradiol above which therapeutic effects are observed, and it is possible that a similar phenomenon (ie, critical threshold) is operational in reproductive hormone-related effects on mood. For example, in women with premenstrual syndrome, a threshold of gonadal steroid levels may exist above which mood instability occurs, and, therefore, ovarian suppression with low level gonadal steroid replacement may produce mood stability. Additionally, there may be a critical threshold of estradiol or DHEA levels below which symptoms develop in some women, and the replacement of these hormones may elevate hormone levels sufficiently to produce a mood-enhancing effect. Third, the rate of change in hormone level may convey information and trigger mood changes in women who have a differential sensitivity to increasing (eg, PMS) or decreasing (eg, perimenopausal or postpartum depression) levels of gonadal steroids. Although basal hormone abnormalities do not characterize most women with reproductive endocrine-related mood disorders or classical mood disorders, diagnosis-related differences in the rapidity of the decline in

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gonadal steroids during the postpartum or during the perimenopause may contribute to the onset of mood symptoms, a phenomenon that would not readily be identified in cross-sectional studies. Gonadal steroid replacement, therefore, could attenuate the rate of change of gonadal steroids in these subjects and prevent the occurrence of depression. Finally, it is possible that a direct psychotropic effect of gonadal steroids may be involved in their antidepressant efficacy. For example, the efficacy of estradiol in perimenopausal depression^{129,130} and reports (in some^{156,157} but not all¹⁵⁸ studies) of estrogen augmenting the therapeutic efficacy of SSRIs suggest that estrogen may be acting pharmacologically, like other antidepressants, to alter the function of the central serotonin system.¹⁷³⁻¹⁷⁵ Roca et al¹⁷⁶ have attempted to identify a possible role of serotonin in the antidepressant efficacy of ERT in perimenopause-related depression by employing the serotonin receptor antagonist metergoline. Perimenopausal depressed women who had previously demonstrated a remission of their mood symptoms on estradiol but not placebo were placed on open estrogen treatment. Subjects were administered metergoline or active placebo (benadryl) in a double-blind, crossover design. Depressive symptoms but not hot flashes returned 24 hours after metergoline administration. These changes in symptoms were not seen after placebo administration. These data suggest that the psychotropic effects of estradiol in depression may be mediated through the serotonin receptor subtypes antagonized by metergoline. The specific mechanisms underlying the therapeutic effects of reproductive therapies await the development of more specific antagonists of receptors for both gonadal steroids and neural systems such as the serotonin system.

Future directions

Advances in reproductive therapies for non-mood-related conditions should further the development of compounds whose pharmacologic actions are more specific and clearly defined and, therefore, will assist in efforts to determine the mechanisms of efficacy of reproductive hormones and their analogues in mood disorders in women. Receptor antagonists are available currently for each of the members of the family of steroid receptors. However, efforts to identify and characterize the mechanisms mediating the antidepressant response to gonadal steroids require the development of gonadal

steroid receptor antagonists that reliably cross the blood-brain barrier and display receptor-subtype and brain-region specificity. Such compounds, for example, will facilitate investigations into the roles of estrogen receptors alpha and beta in the psychotropic actions of estradiol. Indeed, recent work by Krezel et al¹⁷⁷ suggest that estrogen receptor beta, but not alpha, plays a prominent role in anxiety in rodents. Selective gonadal steroid receptor modulators are being developed for each of the gonadal steroid receptors, estrogen alpha and beta, progesterone, and androgen, and will provide a new generation of hormonal therapies that could provide more selective and targeted therapeutic effects. For example, beta-estrogen receptor-selective ligands may have differing effects on cognition than estradiol given the relatively higher concentration of estrogen receptor beta than alpha in the hippocampus.^{178,179} Additionally, selective androgen receptor modulators (SARMs),¹⁸⁰ selective estrogen receptor modulators (SERMs),¹⁸¹ and selective progesterone receptor modulators (SPRMs)^{182,183} may display a more acceptable profile of long-term side effects (eg, lack of activity of SARMs at the prostate¹⁸⁰) and permit their use on a more chronic basis.

A potential advantage of reproductive hormonal therapies over conventional antidepressants is suggested by studies reporting the medical sequelae of depression including disorders of metabolism, the musculoskeletal system, and the cardiovascular system.^{184,185} Given the strong association of some of these disorders with deficient or abnormal reproductive endocrine activity,^{33,186-188} reproductive therapies of depression might prevent or reverse some of the medical sequelae in addition to improving mood. Finally, effects of reproductive therapies on the vascular endothelium and local blood flow may contribute to therapeutic effects of these compounds (eg, estradiol or DHEA) in certain conditions where deficits in the vascular system are thought to mediate the primary mood problem, such as in the vascular depressions described in the late-onset mood disorders.¹⁸⁹

Conclusions

Compared with studies performed in the 1800s and to some extent the 1940s and 1950s, recent trials of reproductive endocrine therapies in mood disorders in women have employed more selective pharmacologic compounds, more rigorous study designs, and in some studies

more homogeneous patient samples. Despite improved methodologies, the effects of gonadal steroids on mood regulation remain inconsistently demonstrated. However, there are compelling data supporting a role for gonadal steroids (and reproductive endocrine mod-

ulators) in the treatment of depression in women. Future studies should be directed to better identify both the clinical predictors and the physiological mechanisms of the psychotropic efficacy of reproductive therapies. □

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Tratamientos con hormonas de la reproducción para los trastornos del ánimo en las mujeres

Desde hace más de un siglo en la medicina ha existido la visión que la función reproductora tanto en los hombres como en las mujeres está íntimamente relacionada con la regulación del ánimo. El siglo XIX fue testigo de una proliferación de informes médicos en que se documentaban los beneficios sobre el ánimo y la conducta luego de manipular médica o quirúrgicamente la función reproductora de las mujeres. Más recientemente, los resultados de diversos estudios sugieren que los esteroides gonadales regulan el ánimo en algunas mujeres. Es así como existe un considerable interés en el potencial papel de las terapias con hormonas de la reproducción en el manejo de la enfermedad depresiva, incluyendo tanto los trastornos del ánimo clásicos como aquellos relacionados con la endocrinología de la reproducción. Se requiere de futuros estudios para determinar predictores de respuesta a terapias hormonales comparadas con agentes antidepresivos tradicionales y también para caracterizar la seguridad a largo plazo y los beneficios de estas terapias.

Traitements hormonaux de la fonction reproductrice utilisés pour les troubles de l'humeur chez la femme

Depuis plus d'un siècle, la médecine a pensé que la fonction reproductrice, aussi bien chez l'homme que chez la femme, était intimement liée avec la régulation de l'humeur. Le XIX^e siècle fut le témoin d'une pléthore de textes affirmant les effets bénéfiques sur l'humeur et le comportement de manipulations médicales ou chirurgicales de la fonction reproductrice féminine. Plus récemment, les résultats de plusieurs études ont suggéré que les stéroïdes gonadiques régulaient l'humeur de certaines femmes. Le rôle potentiel des traitements de la fonction reproductrice présente ainsi un intérêt considérable dans la prise en charge de la maladie dépressive, tant sur le plan des troubles de l'humeur classiques que de ceux liés à l'endocrinologie de la reproduction. Les études à venir devront déterminer les facteurs prédictifs des réponses aux thérapies hormonales comparés aux traitements antidépresseurs classiques et définir la tolérance à long terme et les bénéfices de ces traitements.

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